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Trauma care research and the war on uncertainty

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workforces in inadequately funded programmes—such as those for safe motherhood, child survival, tackling malnutrition, and reducing road traffic injuries—are drained to support better paid global initiatives. International migration of healthcare workers further aggravates the situation.^{11 12} Notably, nine of the 20 countries with the highest emigration of healthcare workers are in sub-Saharan Africa, where the millennium health goals are least likely to be achieved. Evidence clearly shows that density of human resources for health at least partly explains variations in maternal, infant, and child mortalities.¹³ In line with resolutions at the World Health Assemblies in 2004 and 2005, member states are committed to solving this problem, but no real concrete global movement has been initiated so far.

Thirdly, accurate information is needed to monitor progress towards the goals. But most poor countries' health information systems are undeveloped and cannot provide reliable data.

The Global Alliance on Vaccine and Immunization, the Global Fund, and the Health Metrics Network

strongly emphasise the need to strengthen systems for health and health information, but proposals made recently at the Global Fund have not yet yielded much success. Of the 30 proposals for strengthening health service infrastructure, only three were approved, because of the poor quality of the proposals. In addition to strengthening health systems, reducing geographical, sociocultural, and financial barriers to care (such as user fees for services) remains just as important.

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Trauma care research and the war on uncertainty

Improving trauma care demands large trials—and large trials need funding and collaboration

For people aged 5-45 years trauma is second only to HIV/AIDS as a cause of death.^{1 2} Every day world wide over 300 000 people are severely injured, about 10 000 of whom die. Road traffic crashes and violence are the leading causes. The global number of road deaths is forecast to rise by 65% between 2000 and 2020 and the number of violent deaths has increased steadily, with the 20th century being the most violent on record. Despite the best preventive efforts, providing effective trauma care will remain a major challenge for healthcare professionals. There is considerable potential to improve trauma outcomes by using clinical audit to increase the implementation of evidence based interventions in trauma services.³ However, for many trauma care interventions, the balance of risks and benefits is uncertain and they must be assessed in randomised trials before being implemented.

Compared with the disease burden there is a dearth of clinical trials in trauma care and the existing trials are small, contributing to uncertainty about effectiveness (see table).⁴ For example, few if any of the pharmacological treatments for brain and spinal cord injury have ever been proved to be effective.⁵ To avoid random errors, trials must recruit sufficient numbers of patients, implying the need for large international collaborative trials. The CRASH trial, run by the UK's Medical Research Council, was designed to confirm or refute the modest but promising effects of corticosteroids on outcome after traumatic brain injury by recruiting 20 000 patients. The trial was stopped after 10 000 patients had been recruited from 239 hospitals in 49 countries. The effect of corticosteroids was a highly significant relative increase of 18% in all cause mortality.⁶ It has been estimated that 10 000 patients with head injuries may have died because of the inap-

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Disease burden and evidence from controlled trials for main categories of human disease in sub-Saharan Africa

Disease category	Burden of disease in 2000 (1000 disability adjusted life years)	No of trials	No of participants	Ratio of burden of disease (1000 disability adjusted life years)	
				Per trial	Per participant
Malignant neoplasms	8114	46	128 786	176	0.06
Nutritional deficiencies	8389	105	111 922	80	0.07
Infectious diseases	131 327	540	813 305	243	0.16
Conditions arising during perinatal period	18 700	30	28 381	623	0.66
Cardiovascular diseases	13 390	99	5648	135	2.37
Respiratory diseases	9037	33	3320	274	2.72
Congenital anomalies	5224	2	1321	2612	3.95
Neuropsychiatric conditions	15 788	41	3580	385	4.41
Injuries	58 352	31	2887	1882	20.21

propriate administration of corticosteroids over the past 30 years.⁷

Large international trials, such as the CRASH trial, also have advantages when it comes to disseminating results. Small trials can remain unpublished, contributing to publication bias. This is less likely with large trials.⁸ In international trials collaborators around the world have an investment in the results and disseminate them locally. Press releases sent by the national coordinators ensured that the results of the CRASH trial were reported in newspapers in over 20 countries. Also, participating hospitals are more likely to implement the results.⁹

There are several obstacles to conducting large trauma trials, some relating to the subject—trauma—and some common to all large trials. Funding for trauma research is less than for almost any other cause of human suffering. A WHO study compared the level of research funding with current and projected (2020) disease burdens.¹⁰ The results showed clearly the relative underfunding of research on road traffic injuries.

Doctors in many countries would collaborate in international trauma trials but there are no well established ways for bringing clinical trials to their attention. Investigators try to get editorials about trials published and will present trial protocols at conferences, but some journals are reluctant to advertise trials or are unwilling to publish editorials when the authors have a stake in the trial they are writing about, which they necessarily do.

People conducting large trials must now negotiate a large number of regulatory, ethical, and logistic hurdles, not least the good clinical practice (GCP) requirements, which are geared towards the development of drugs.¹¹ Without a secure evidence base for doing so, the demands of the good clinical practice procedures are being indiscriminately applied not just to the drug industry trials they were designed for but to clinical trials of all types of interventions and to independent investigator-led non-commercially funded studies as well.

For example, the GCP emphasis on the monitoring and auditing of trial data might not be the best use of the scarce resources for large trials, as well as generating thousands of miles of unnecessary travel, when statistical approaches to monitoring may be more effective and more appropriate. Trauma care trials also have special circumstances and few countries have legislation in place to handle them. These trials take place in emergency situations,

require quick decisions for early interventions, and include patients who are unable to give informed consent (and who usually are not accompanied by anyone who can make decisions for them). Few countries have legislation in place for the special circumstances in such trauma trials, and, as a result, trauma patients are unfairly denied the benefits of medical research. Servicing the numerous ethics committees involved in a large multicentre trial also has huge resource implications and can involve long delays. The CRASH trial collaborators completed over 500 ethics application forms.

University promotion is often related to the number of publications on which the researcher is first author. This encourages competition rather than collaboration. Collaborative trials often cite the collaborative group rather than individuals. Some journals accept this model but problems still arise in indexing.¹² Citing as authors only a writing group is not a fair way of apportioning responsibility or credit. Reward systems favour small trials with named authors even though this increases the risk of inappropriate inferences due to the play of chance and publication bias.

There is an urgent need to improve the evidence base for trauma care. Large trials can provide important answers, but to wage war on uncertainty we need large collaborations of equals rather than small groups of individualists. Doctors internationally can join these collaborations but we need ways to bring trials to their attention, to reduce the regulatory burden, and to reward collaboration. Most importantly, the mismatch between the funding for trauma research and the burden of injury must be addressed.

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Competing interests: IR, HS, and PE work on the CRASH-2 trial, a large international trauma trial, and are seeking further funding for this trial.

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Persistent high stroke mortality in Bangladeshi populations

Novel hypotheses to explain this need testing urgently

Censuses in 1981, 1991,¹⁻³ and 2001 (Wild et al. Persistence of substantial inequalities in cardiovascular disease mortality by country of birth in England and Wales 2001-2003. Unpublished manuscript). have shown that, among Bangladeshi-born men living in the United Kingdom, the standardised mortality ratio for stroke is two to three times the population average, with less marked but important excesses in Bangladeshi-born women. There has been little progress in understanding the reasons for this variation, let alone in identifying approaches to improve outcomes. Lessons learnt about stroke among British Bangladeshis may well apply to other populations at high risk, including Indians and Pakistanis, whose excess stroke mortality is not quite so high. In addition, such evidence could be highly relevant to reducing health inequalities.

Is the excess mortality from stroke in Bangladeshis explained by a higher case fatality ratio? Interim analysis of data from the south London stroke register shows no age adjusted difference in survival between Bangladeshis and white Europeans (albeit based on a small population), but does find an almost doubled age adjusted incidence of stroke in Bangladeshis (Smeeton N, personal communication of unpublished data from Stewart et al⁴). Thus, these mortality data seem to reflect a real excess that cannot be explained by a higher case fatality.

To what extent, then, can these differences be explained by an excess of risk factors for stroke? Hypertension is the most important potential explanation, but studies conducted in east London and Newcastle found Bangladeshi adults to have on average a mean systolic blood pressure that is 10 mm Hg lower than that of white Europeans.^{5,6} These regional findings have been confirmed by national data from the Health Survey for England 1999 and a recent systematic review.^{7,8} Total and low density lipoprotein cholesterol concentrations are also comparatively low among Bangladeshis.^{5,6} Bangladeshi men tend, however, to have a high prevalence of diabetes, smoking, physical inactivity, and high serum

triglyceride concentrations, and low serum high density lipoprotein cholesterol concentrations.^{2,5-7} For women, the burden from these risk factors is also high, except for smoking, which is uncommon.^{2,6} Bangladeshis are also among the poorest of Britain's populations.

The Framingham stroke model and European SCORE model both predict comparatively low rates of stroke and cerebrovascular disease. For example, in Bangladeshi men the Framingham model predicts the incidence of stroke to be 52% (95% confidence interval 35% to 77%) of that for the white European population.³ We need to look beyond classic stroke risk factors.

We suggest four specific lines of investigation that warrant consideration—squatting and straining at stool, vitamin D deficiency, infection, and the combined impact of smoking and tobacco chewing. Chakrabarti's work on three groups—patients with stroke, healthy volunteers, and hypertensive patients—has identified squatting as a potential causal or precipitating factor for stroke.⁹ Squatting is a fairly common posture among South Asians and is known to raise blood pressure by about 4-8 mm Hg with a sustained effect during the period of squatting; importantly, this blood pressure rise is greatest in the central vasculature.

Vitamin D deficiency is very common among Bangladeshis in London, because of a diet lacking fish, ghee, and eggs among both sexes and lack of exposure to sunlight, particularly among women.¹⁰ Vitamin D deficiency may raise the risk of stroke by increasing insulin resistance and hypertension, or may worsen outcomes after stroke by impairing neuroprotective mechanisms.

Chronic inflammation is a well recognised risk factor for stroke. A recent large case series reported that the incidences of both myocardial infarction and stroke were significantly raised in the few days after acute infection, particularly of the respiratory tract.¹¹ Many Bangladeshis in the UK live in overcrowded households, with consequent increased risk of respira-

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